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Risk factors for severe renal disease in Bardet-Biedl syndrome.

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Abstract

Bardet-Biedl syndrome is a rare autosomal recessive multi-system disease characterised by retinal dystrophy, renal malformation, obesity, intellectual disability, polydactyly and hypogonadism. Nineteen disease causing genes (*BBS1-19*) have been identified of which mutations in *BBS1* are most common in North America and Europe.

A hallmark of the disease, renal malformation is heterogeneous and is a cause of morbidity and mortality through the development of chronic kidney disease. We studied the prevalence and severity of chronic kidney disease in the largest reported cohort of patients with Bardet-Biedl syndrome-related renal disease, further elucidating the phenotype and identifying risk indicators.

Thirty six per cent of children and 42% of adults had chronic kidney disease (CKD). End stage renal disease (CKD4-5) was present in 8% of adults. In childhood, CKD was primarily detected within the first year of life and end stage renal disease was present in 6%. Albuminuria was associated with severe renal disease (estimated glomerular filtration rate <45 mls/min/1.73m^2). Fifty one percent of patients had structural renal abnormalities on ultrasonography and 35% were hypertensive. These risk factors also correlated statistically with CKD3b-CKD5.

Genotype and mutation type were statistically significant risk indicators. Mutations in *BBS1* or two missense mutations were associated with less severe or lack of chronic kidney disease in comparison to mutations in *BBS10* or two truncating mutations.

This study identifies risk factors to be considered in genetic counselling and presents paediatric and adult nephrology management schemes for BBS.

Introduction

Bardet-Biedl syndrome (BBS) is a rare autosomal recessive ciliopathy characterised by rod cone dystrophy, renal malformations, learning difficulties, obesity, post-axial polydactyly and hypogonadism.[1] Nineteen disease causing genes have been identified (*BBS1-BBS19*) in the last two decades. BBS genes code for proteins that localise to the cilia or the basal body and are thought to be involved in cilia development and maintenance[2]. Mutations in BBS genes lead to defective cilia. Sequencing of known disease causing genes confirms a clinical diagnosis of BBS in around 80% of patients[2]. Variable expressivity is a hallmark of BBS and both inter- and intrafamilial phenotypic variation is observed.[2]

Structural renal and urinary tract anomalies and renal dysfunction is a cause of considerable morbidity and reported to affect 53-82% of patients with BBS.[2-4;4-6] The primary renal phenotype is highly variable ranging from cystic tubular disease, dysplastic renal disease and focal segmental glomerulosclerosis to concentrating defects.[3-7] Lower urinary tract dysfunction is observed in many patients and may have upper renal tract sequelae.[8] It is thought that ciliary dysfunction leads to disturbance of the non-canonical Wnt signalling pathway which may contribute to the development of cystic kidney disease classically associated with BBS.[2] Secondary renal disease may occur as a consequence of hypertension and diabetes which are frequently observed in this population.

The high frequency of renal disease in BBS is a cause of great anxiety among patients due to the devastating effect this can have on quality of life, morbidity and mortality.[4-6] This study examines renal disease in the largest reported cohort of BBS

patients and identifies indicators of disease which are directly relevant to patient management and clinical stratification.

Results

Overview of the BBS population

Three hundred and fifty patients attended the adult and paediatric national BBS clinics in Birmingham and London over a four year period (2010-14). The patient population ranged in age from birth to 60 years old, with a peak frequency in the five to nine year old category, and with few older adults (figure 1).

Diagnosis was based on clinical phenotyping. Molecular confirmation of the diagnosis was achieved in 77% (n=265) of patients on sequencing 13 disease related genes.

The distribution of genotypes is demonstrated in figure 2. For the purpose of statistical analysis mutation type was classified according to severity. One hundred and sixteen patients had two missense mutations, 108 had two truncating mutations (nonsense or frameshift), 33 had a combination of missense and truncating mutations and the remaining eight patients had other mutation combinations such as exon deletions and splice site mutations.

Age of onset of renal disease

We were able to retrospectively obtain the earliest recorded age of onset of CKD stage[9] in 58 paediatric patients attending the BBS clinic (figure 3). All paediatric

patients with end stage renal failure (ESRF; CKD4-5) were diagnosed before the age of 5. The majority of patients with any stage of CKD presented before the age of 10. Since the peak referral age to the clinic is late childhood, later recorded onset of CKD is likely to reflect significant ascertainment bias as patients may have asymptomatic renal disease and no previous renal sonography.

Observations from the national BBS clinics suggest that patients either develop ESRF in childhood or maintain normal or near-normal renal function into adulthood. Figure 4 demonstrates the age at which ESRF was first identified in children and adults and largely supports this finding. All patients with primary renal disease developed ESRF by the age of 15 (n=10). Although under-reported, 6% of the adult BBS population report urological complications requiring specialist management. Urological abnormalities include neuropathic bladder, vesico-ureteric reflux, urinary incontinence and bladder outflow obstructions.

Prevalence of chronic renal disease

Estimated GFR (eGFR) results were available for 194 adults and 145 paediatric patients. Seventy per cent of adult patients had at least two eGFR readings. The frequency of each stage of CKD in adults and children is demonstrated in figure 5 where it is present in 42% and 36% respectively.

Genotype and mutation type analyses in adults with BBS revealed statistically significant correlations with the presence of severe renal disease defined as CKD stage 3b to 5 (eGFR<45 ml/min/1.73m^2). Univariable logistical regression analysis indicated that mutations in *BBS2*, *BBS10* and *BBS12* were more likely to be

associated with severe renal disease than mutations in *BBS1* (p values: 0.02, 0.0004, 0.03 respectively) (table 1). Univariable logistical regression analysis of mutation type revealed that truncating mutations and truncating/ missense mutations were statistically associated with severe renal disease in comparison to two missense mutations (p values= 0.0003, 0.02 respectively) (table 1). Multivariable regression analysis including genotype, mutation type, age, hypertension, type 2 diabetes, and BMI, revealed that mutations in *BBS10* are independently associated with severe renal failure (p=0.028) (table 2).

Proportional frequencies of CKD stages 2, 3, 4 and 5 in adults were compared for the commonest genotypes *BBS1* and *BBS10* as outlined in figure 6a. Patients with *BBS1* mutations are more likely to be disease free or have early stage CKD. Mutations in *BBS10* were more frequently represented with increasing stage of CKD. Of note, patients attending our clinics with mutations in *BBS1* are statistically significantly older than those with mutations in *BBS10* (*p*=0.0011). It is unknown why this may the case.

The effect of mutation type on proportional frequencies of CKD stages 2-5 was also assessed. Patients with all genotypes were included and mutation types classified as either missense or truncating (nonsense or frameshift mutations) or other mutations. Patients with two missense mutations were compared to patients with two truncating mutations (figure 6b). Having two missense mutations was associated with a disease free state or early stages of CKD. Patients with two truncating mutations were more likely to have ESRF.

Previous research indicates that the recurring missense mutation M390R in *BBS1* may be hypomorphic.[10;11] We assessed this by comparing adult patients who were

homozygous for M390R to patients with all other genotypes (figure 6c). Only one patient homozygous for M390R had progressed beyond stage 3 CKD. The patient presented following renal transplant aged 23 to our service and the cause of renal failure was unclear although presumed to be a result of BBS.

We assessed for the presence of micro- and macroalbuminuria analysing urinary albumin/creatinine ratios as a proxy for nephron impairment. Urinary albumin/ creatinine ratios were available for 139 adult and paediatric patients. Seven (5%) had proteinuria (defined as urinary albumin/ creatinine >30 mg/mmol) and 32 (28%) had microalbuminuria (defined as urinary albumin/ creatinine >3.5 mg/mmol[12]). This could be matched to an eGFR in 119 patients. There was a statistically significant correlation between severe renal disease and urinary albumin/ creatinine ratios (p= 0.006). The sample size was inadequate for correlation with genotype and mutation type.

Presence of structural abnormalities

One hundred and seventy seven ultrasound reports from the entire cohort were available for our assessment. Eighty seven were unremarkable and 90 revealed structural defects. Abnormalities were categorised as atrophic/scarring, echogenic or loss of corticomedullary differentiation, cystic or dysplastic, other developmental abnormality or hydronephrosis as seen in figure 7. Where several abnormalities were present the predominant structural defect is reported. On assessing genotype correlations (*BBS1* versus *BBS10*) no association with the presence of structural abnormality was identified (p=0.188).

Correlating the presence of all cause structural abnormality in adults with CKD staging revealed a strong correlation with CKD at stage 3b-5 (p=0.039). All patients with a reported renal ultrasound scan and severe renal disease had a detectable structural abnormality (n=7).

Ultrasound reports from 39 paediatric patients with known renal structural abnormalities who had both antenatal and postnatal sonography failed to identify the anatomical aberration prenatally in 14 patients (36%).

Five paediatric patients had abnormal antenatal renal ultrasound reports and normal postnatal sonography. In all cases non-specific echogenicity was reported antenatally and no specific structural abnormalities were detected.

In this cohort 30 patients presented with sonographic evidence of cystic kidney disease which is classically associated with BBS. Twenty four of these patients had molecular confirmation of BBS. Patients with mutations in *BBS1* and *BBS10* accounted for the majority of genotypes represented (42% and 21% respectively).

Hypertension and diabetes

Thirty five per cent of adult patients (n=67) in this cohort were found to be hypertensive. There is a statistically significant correlation between severe renal failure and the presence of anti-hypertensive medication (p=0.003) (table 1) although it is not clear if this is an independent risk factor or if it is because antihypertensive medication is prescribed as a part of the management of CKD. There was a significant association between the presence of hypertension and albuminuria (p=0.0009). Although patients with mutations in *BBS10* make up only 20% of

patients with a known mutation they account for 50% (n=3) of those adult patients with molecular confirmation of BBS aged under 25 receiving anti-hypertensive medication. The most commonly prescribed antihypertensive medications were ACE inhibitors (52%) followed by diuretics (21%), calcium channel blockers (15%), beta blockers (8%) and angiotensin receptor blockers (3%).

Fifteen per cent of adult patients (n=28) were on hypoglycaemic medication. There was no statistically significant association with CKD (p=0.471).

Discussion

To our knowledge this is the largest reported study characterising the renal phenotype in BBS. The age distribution of our patient population is most likely a reflection of a number of factors affecting patient referral. Children are often referred to the service following the onset of visual decline which typically occurs towards the end of the first decade of life, accounting for the high frequency of children aged five to nine years old. Many children presenting in the first year of life are siblings of patients known to the service. The clinical service has been in operation since 2010 and patients over the age of 60 may not have a known diagnosis of BBS as familiarity with the syndrome has only increased in the last two decades. The variation of genotypes presented in this study reflects the UK BBS population and is similar to that observed by others in Europe and North America.[13;14]

Our study suggests that the onset of primary renal disease in children predominantly occurs in infancy. For many adult patients it was difficult to accurately determine the age of onset of renal disease since patients with CKD are managed locally with an

annual specialist BBS review. A striking observation is the relatively modest difference in prevalence of ESRF (CKD4-5) between adults (8%) and children (6%) (figure 5). This supports our hypothesis that patients with BBS primarily either develop ESRF in childhood or remain entirely or relatively free of severe renal disease. The small proportion of adult onset severe renal disease may relate to co-morbidities associated with BBS such as urological complications, hypertension, obesity and diabetes. These are potentially modifiable risk factors which should be managed appropriately.

The prevalence of CKD in this cohort is lower than anticipated based on previous estimates[3]. Forty two per cent of adults have CKD stage 2-5 and only 8% of adult patients develop CKD3b-5. There appears to be both genotype and mutation type correlations with CKD with increased risk of developing CKD3b-5 for those patients who have truncating mutations and mutations in *BBS10*. This is in keeping with a previous study indicating similar findings for cardiovascular risk factors in this group.[15] Furthermore, only one of the patients in this study with homozygous *BBS1* M390R mutations developed ESRF. *BBS1* M390R is the most common mutation observed in the BBS population in Europe and Northern America and patients homozygous for M390R make up a significant proportion of the patient population (45% of the UK population are homozygous or heterozygous for this mutation, own unpublished data). This significant subgroup of patients could be counselled regarding their lower risk of progressing to ESRF.

Guidelines for the management of BBS recommend that every patient should have a baseline renal ultrasound examination to assess for the presence of any structural abnormalities.[16] Although some patients who have abnormal renal ultrasound scans do not go on to develop CKD there is a statistically significant correlation between

structural abnormalities and CKD. This study validates the requirement for a baseline postnatal renal ultrasound scan following a diagnosis of BBS. Structural abnormality should alert clinicians that close monitoring is required to identify any deterioration in renal function. Anecdotal reports of structural renal abnormalities present antentally and absent on postnatal sonography could not be confirmed in this study.

One report[17] suggests that mutations in *BBS10* are associated with antenatal severe cystic kidney disease which is incompatible with life. In this study, the prevalence of *BBS10* mutations among patients presenting with postnatal sonographic evidence of cystic kidney disease (21%, n=5) was consistent with that of the overall study population (20%). The authors are not aware of a higher rate of pregnancy losses in families with *BBS10* mutations.

It has previously been suggested that proteinuria is consistently absent in BBS – associated renal disease.[18] This study demonstrates the co-existence of proteinuria and CKD and the correlation between severe renal disease and albuminuria.

Hypertension is a common feature of BBS and we have previously reported on the high prevalence of antihypertensive medication in this group. Patients with mutations in *BBS10* are disproportionately represented in the younger age groups compared to patients with mutations in *BBS1*.[15]

In summary, this study maps the prevalence of renal disease in BBS and characterises the highly variable renal phenotype. We have identified risk indicators as well as potentially protective factors for renal disease. Adults who harbour missense mutations in *BBS1*, have no albuminuria and have normal renal ultrasound scans in adulthood are less likely to develop ESRF. Patients with truncating mutations in *BBS10*, albuminuria and abnormal renal ultrasound scans are at

significantly increased risk of ESRF compared to the general BBS population. Primary renal disease as consequence of BBS appears to present in early childhood.

The evidence presented here could have a direct clinical implication for BBS patients. The presence or absence of risk factors should be considered when counselling patients and may be used to stratify the clinical service. Previous recommendations advise that patients should be reviewed by a nephrologist annually unless CKD is present in which case closer monitoring is required. Based on this study the authors recommend risk factor- dependent tiered adult and paediatric nephrology management approaches as outlined in figures 8a and 8b. Adults with the lowest risk of renal disease could receive community nephrology follow up and low risk children could be seen less frequently in specialist clinics. All patients with end stage renal disease require frequent specialist follow up and those with identifiable risk factors or early stable renal disease (CKD1-3) warrant annual specialist follow up. A multi-national study could facilitate the development of a statistical renal risk calculator for this unique population.

Concise methods

Patients

The following renal parameters were ascertained retrospectively for all 350 patients attending the national BBS clinics: known history of renal disease, stage of CKD if present, any abnormalities noted on renal ultrasound scanning, estimated glomerular filtration rate (eGFR), renal function tests and relevant concomitant factors including presence of hypertension, diabetes and obesity. All blood and urinary tests were

completed following a six hour starvation period. The Modification of Diet in Renal disease (MDRD) formula was applied to estimate glomerular filtration rate in all adults in keeping with its common use for patients with obesity and diabetes in the general population[19]. Estimated GFR for the paediatric population was calculated according the Schwarz-Haycock formula (height (cm) x 31/ creatinine (µmol/l)). Adults were categorised as hypertensive if they were on anti-hypertensive medication, had a blood pressure greater than 140/90 mmHg or a blood pressure greater than 130/80 in combination with albuminuria. Patients were predominantly of Caucasian and South East Asian origin and referrals were made primarily from the British national patient support group, clinical geneticists and ophthalmologists in the United Kingdom.

Mutation analysis

Mutation analysis was undertaken through the UK national BBS gene panel which encompasses 11 BBS genes including *BBS1- BB10* and *BBS12* as well as two BBS associated genes *MKS1* and *ALMS1*.

Statistical analysis

Genotype-phenotype analysis was targeted to patients with mutations in the two most commonly affected genes: *BBS1* and *BBS10*, as well as the less common genotypes *BBS2* and *BBS12* where adequate sample sizes were available. Correlation with mutation type was also assessed. Patients with two known missense mutations were compared with two known truncating (nonsense or

frameshift) mutations and a combination of missense/truncating mutations. The nonparametric Mann–Whitney U test was performed to assess differences in median age for genotypes *BBS1* and *BBS10*. For the purpose of genotype and mutation type analysis children were not included since renal failure appears to occur and progress primarily in childhood, hence CKD stage was not considered to be stable until adulthood. Multivariable regression analysis was applied to evaluate genotype-phenotype analysis and assess the effect of confounders on chronic renal disease. The relative burden of each risk factor was described in odds ratios. Statistical analyses were conducted in R (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Retrieved from: http://www.R-project.org/). A 5% confidence level was considered statistically significant. All tests were two tailed.

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Statement of competing financial interests

The authors declare that they have no conflicts of interest.

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Figure legends

Figure 1. Age distribution of patients

Figure 2. Figure 2. Distribution of genotypes

Figure 3. Age and CKD stage at which renal disease was first noted in paediatric patients with BBS (n=58)

Figure 4. Age at onset of end stage renal disease (CKD4-5) and primary pathology (n=28)

Figure 5. Distribution of chronic kidney disease stages in adults and children

Figure 6. a. Percentage distribution of chronic kidney disease stages in adults. Mutations in *BBS1* versus *BBS10*; b. Percentage distribution of chronic kidney disease stages in adults. Missense mutations versus truncating mutations. c. Percentage distribution of chronic kidney disease stages in adults. *BBS1* M390R vs other known genotypes. Absolute numbers are indicated in each column.

Figure 7. Prevalence of structural abnormalities detected on sonography

Figure 8. a. Nephrology management of adult BBS patients. b. Nephrology management of paediatric BBS patients.

Table 1. Univariable logistical regression analysis of risk factors for severe renal disease in adults. (eGFR<45 ml/min/1.73 m^2). All statistically significant findings are highlighted in bold.

Risk factors for severe renal disease				
Risk factor	**Odds ratio**	**Confidence interval** 2.5%	97.5%	**P value**
Genetic factors				
Genotype				
BBS1 mutation	*Reference*			
BBS2 mutation	4.4	1.28	15.19	**0.016**
BBS9 mutation	2.4	0.12	17.74	0.458
BBS10 mutation	7.4	2.49	23.32	**0.0003**
BBS12 mutation	5.9	1.08	28.39	**0.0278**
Mutation type				
Two missense mutations	*Reference*			
Two truncating mutations	11.4	3.9	41.8	**3.43e-05**
Missense/truncating	6.3	1.5	28.6	**0.0116**
Diabetes	0.62	0.14	0.99	0.471
Hypertension	5.43	2.21	14.29	**0.003**
BMI	1.04	0.96	1.10	0.321
Age	1.02	0.99	1.96	0.154
Urinary protein				
Urinary albumin/creatinine ratio	1.07	1.02	1.20	**0.006**
Structural abnormalities				
USS abnormality	1.32	1.02	1.72	**0.039**

Table 2. Multivariable logistical regression analysis of risk factors for severe renal disease in adults. (eGFR<45 ml/min/1.73 m^2). All statistically significant findings are highlighted in bold.

Risk factors for severe renal disease				
Risk factor	**Odds ratio**	**Confidence interval** 2.5%	97.5%	**P value**
Genotype				
BBS1 mutation	*Reference*			
BBS2 mutation	9.5	0.22	572.2	0.219
BBS10 mutation	189.9	3.73	83960.35	**0.028**
Mutation				
Two missense	*Reference*			
Two truncating	3.43	0.26	107.22	0.386
Missense/ truncating	34.81	0.57	5145.83	0.095
Diabetes	0.28	0.002	6.51	0.503
Hypertension	22.04	0.42	8314.86	0.184
BMI	0.88	0.73	1.08	0.145
Age	1.05	0.89	1.28	0.537
Gender	0.61	0.03	9.05	0.721